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Ambient Water Quality Criteria: Thallium

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THALLIUM

Ambient Water Quality Criteria

Criteria and Standards Division
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CRITERION DOCUMENT

THALLIUM

CRITERIA

Aquatic Life

For freshwater aquatic life, no criterion for thallium can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

For saltwater aquatic life, no criterion for thallium can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

Human Health

For the protection of human health from the toxic properties of thallium ingested through water and contaminated aquatic organisms, the ambient water criterion is 4 ug/l.

BIBLIOGRAPHIC INFORMATION

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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for thallium. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no , ...

KEYWORDS: *Water quality, *Toxicology, *Thallium, *Water pollution effects(Humans), *Water pollution effects(Animals), *Toxic substances, *Water pollution effects(Plants).

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Introduction

Thallium is an element having the chemical symbol Tl and is a soft, malleable, heavy metal with a silver-white luster (Lee, 1971). Industrial uses of thallium include the manufacture of alloys, electronic devices, and special glass. Many thallium-containing catalysts have been patented for industrial organic reactions (Zitko, 1975). Production and use of thallium and its compounds approximated 680 kg in 1976 (U.S. Dep. Interior, 1977; Zitko, 1975).

Thallium has an atomic weight of 204.37, a melting point of 303.5 degrees C, a boiling point of 1,457 $\pm$ 10 degrees C, and a specific gravity of 11.85 at 20 degrees C (Weast, 1975). Thallium exists in either the monovalent (thallous) of trivalent (thallic) form, the former being the more common and stable and therefore forming more numerous and stable salts (Hampel, 1968). Thallic salts are readily reduced by common reducing agents to the thallous salts (Standen, 1967).

Thallium is chemically reactive with air and moisture, oxidizing slowly in air at 20 degrees C and more rapidly as the temperature increases, with the presence of moisture enhancing this reaction (Standen, 1967). Thallous oxide, formed by oxidizing the metal at low temperatures, is easily oxidized to thallic oxide or reduced to thallium. Thallous oxide is a very hygroscopic compound and has a vapor pressure of 1 mm Hg at 580 degrees C (Lee, 1971). Thallous hydroxide

is formed when thallium contacts water containing oxygen (Hampel, 1968). While thallium itself is relatively insoluble in water (Windholz, 1976), thallium compounds exhibit a wide range of solubilities, as shown in Table 1.

TABLE 1

Water solubilities of some thallium compounds (Standen, 1967)

Compound	Molecular Formula	Solubility (mg/l)	Temperature (degrees C)
Thallium sulfide	Tl_2S	220	20
Thallium bromide	TlBr	240	0
Thallium chromate	Tl_2CrO_4	300	60
Thallium chloride	TlCl	2,100	0
Thallium sulfate	Tl_2SO_4	27,000	0
Thallium carbonate	Tl_2CO_3	42,000	15
Thallium bromide	TlBr	160,000	20
Thallium hydroxide*	TlOH	259,000	0
		520,000	40
Thallium fluoride	TlF	780,000	15

*(Weast, 1975)

The average concentration of thallium in seawater has been reported to be 10 ng/l (Bowen, 1966). Analyses of U.S. river water during 1958 and 1959 reported no thallium at detection limits (Durum and Haffty, 1961; Faber and Bryson, 1960). More recent analyses of household tap water samples have detected thallium at an average concentration of less

than 1 µg/l in less than one percent of all samples.

Thallium is harmful to a wide variety of organisms at low concentrations. In the aquatic environment, thallium has been demonstrated to be chronically toxic to fish at concentrations as low as 20 µg/l and to bioconcentrate by a factor of up to 130. In non-aquatic organisms, including humans, symptoms of acute exposure to thallium include alopecia, ataxia, and tremors (Reed, et al. 1963), occasionally leading to irreversible coma and death (Bank, et al. 1972).

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

The data base for the effects of thallium on freshwater organisms does not permit any determination of the effects of water quality on toxicity. There are sufficient data to indicate that thallium can be chronically toxic to fish at concentrations as low as 20 µg/l. Algae are also sensitive with effects as low as 100 µg/l.

Acute Toxicity

The bluegill (U.S. EPA, 1978, and Dawson, et al. 1977) appears to be extremely resistant to thallium under static test conditions with adjusted 96-hour LC50 values of 72,164 and 66,151 µg/l, respectively (Table 1). The fathead minnow was tested (U.S. EPA, 1978) under flow-through conditions with measured concentrations and the 96-hour LC50 is 860 µg/l. Zitko, et al. (1975) exposed Atlantic salmon for as long as 2,600 hours and observed 40 and 70 percent mortality at approximately 20 and 45 µg/l (Table 6). Mortality occurred throughout the test.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] and the Methodology Document in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

The geometric mean LC50 value for the bluegill and fathead minnow is 7,708 µg/l (Table 1). After division by the sensitivity factor (3.9) this becomes 2,000 µg/l. However the Guidelines state that if a 96-hour LC50 value derived from a flow-through test with measured conentrations is lower than the geometric mean, the former becomes the Final Acute Value. In this instance the 96-hour LC50 (860 µg/l) for the fathead minnow becomes the Final Fish Acute Value.

The 48-hour EC50 for Daphnia magna is 1,846 µg/l (Table 2). This test result, when divided by the sensitivity factor (21), results in a Final Invertebrate Acute Value of 88 µg/l; this concentration also becomes the Final Acute Value.

Chronic Toxicity

An embryo-larval test has been conducted (U.S. EPA, 1978) with the fathead minnow and adverse effects were observed at the lowest thallium concentration of 40 µg/l (Table 3). This datum results in a Final Fish Chronic Value of less than 6 µg/l. The difference between the acute (96-hour LC50 = 860 µg/l) and chronic effects (less than 40 µg/l) of thallium on the fathead minnow is at least 21. No chronic data are available for freshwater invertebrate species.

Plant Effects

There was a 40 percent inhibition of oxygen evolution by the alga, Chlamydomonas reinhardi, exposed to a concentration of 40,800 µg/l (Table 4). The 96-hour EC50 values for chlorophyll a inhibition and cell number are 110 and 100 µg/l, respectively. The lower of these concentrations becomes the Final Plant Value.

Residues

Muscle tissue of Atlantic salmon (Zitko, et al. 1975) bioconcentrated thallium to a concentration 130 times that in the water (Table 5). The bluegill (whole body) bioconcentrated thallium 34 times and the tissue half-life was greater than 4 days (U.S. EPA, 1978).

Miscellaneous

The long-term effects (Table 6) of thallium on mortality of Atlantic salmon were discussed earlier. No other effects were observed at concentrations close to those affecting the salmon.

CRITERION FORMULATION

Freshwater Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures. All concentrations herein are expressed in terms of thallium.

Final Fish Acute Value = 860 µg/l

Final Invertebrate Acute Value = 88 µg/l

Final Acute Value = 88 µg/l

Final Fish Chronic Value = less than 6.0 µg/l

Final Invertebrate Chronic Value = not available

Final Plant Value = 100 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = less than 6.0 µg/l

0.44 x Final Acute Value = 39 µg/l

No freshwater criterion can be derived for thallium using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

Table 1. Freshwater fish acute values for thallium

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Fathead minnow, *Pimephales promelas*	FT	M	96	860	860	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	R	U	96	132,000	72,164	Dawson, et al. 1977
Bluegill, *Lepomis macrochirus*	S	U	96	121,000	66,151	U.S. EPA, 1978

* S = static, FT = flow-through, R = renewal

** U = unmeasured, M = measured

Geometric mean of adjusted values = 7,708 µg/l $\frac{7,708}{3.9}$ = 2,000 µg/l

Lowest value from a flow-through test with measured concentrations = 860 µg/l

Table 2. Freshwater invertebrate acute values for thallium (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Cladoceran, *Daphnia magna*	S	U	48	2,180	1,846

* S = static

** U = unmeasured

Geometric mean of adjusted values = 1,846 µg/l $\frac{1,846}{21}$ = 88 µg/l

Table 3. Freshwater fish chronic values for thallium (U.S. EPA, 1978)

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)
Fathead minnow, Pimephales promelas	E-L	<40	<20

* E-L = embryo-larval

Geometric mean of chronic values = <40 µg/l $\frac{<40}{6.7}$ =<6.0 µg/l

Lowest chronic value = <20 µg/l

Table 4. Freshwater plant effects for thallium

Organism	Effect	Concentration (ug/l)	Reference
Alga, *Chlamydomonas reinhardi*	40% inhibition of oxygen evolution	40,800	Overnell, 1975a
Alga, *Selenastrum capricornutum*	96-hr EC50 for chlorophyll *a* inhibition	110	U.S. EPA, 1978
Alga, *Selenastrum capricornutum*	96-hr EC50 for cell number	100	U.S. EPA, 1978

Lowest plant value = 100 µg/l

Table 5. Freshwater residues for thallium

Organism	Bioconcentration Factor	Time (days)	Reference
Atlantic salmon (juvenile), *Salmo salar*	130*	12.5	Zitko, et al. 1975
Bluegill, *Lepomis macrochirus*	34	28	U.S. EPA, 1978

* Muscle tissue.

Table 6. Other freshwater data for thallium

Organism	Test Duration	Effect	Result (ug/l)	Reference
Atlantic salmon (juvenile), Salmo salar	2,600 hrs	LC40	~20	Zitko, et al. 1975
Atlantic salmon (juvenile), Salmo salar	2,600 hrs	LC70	~45	Zitko, et al. 1975
Fathead minnow, Pimephales promelas	7 days	LC50	800	U.S. EPA, 1978
Frog (egg), (unidentified)	56 days	Mortality	409	Dilling & Heale, 1926

SALTWATER ORGANISMS

Introduction

There are a variety of test results with thallium and saltwater organisms conducted using static test procedures. No adverse effects were observed lower than approximately 1,000 µg/l. However, adverse chronic effects on freshwater organisms occurred at much lower concentrations and this suggests a need for long term testing with saltwater species.

Acute Toxicity

The sheepshead minnow (U.S. EPA, 1978) and the tidewater silverside (Dawson, et al. 1977) are similarly sensitive with unadjusted LC50 values of 20,900 and 24,000 µg/l, respectively (Table 7). The Final Fish Acute Value derived from these data is 3,300 µg/l.

Mysidopsis bahia (U.S. EPA, 1978) was more sensitive than the tested fish with an unadjusted LC50 value of 2,130 µg/l (Table 8). The Final Invertebrate Acute Value is 37 µg/l; this concentration also becomes the Final Acute Value.

Chronic Toxicity

The chronic effect of thallium on saltwater organisms has not been reported.

Plant Effects

There was a 50 percent inhibition of two algal species at thallium concentrations of 4,080 and 51,200 µg/l (Table 9). The Final Plant Value is, therefore, 4,100 µg/l.

Residues

Zitko and Carson (1975) observed bioconcentration factors of 18 and 12 for the soft shell clam and blue mussel, respectively (Table 10). These results indicate that saltwater clams and mussels do not bioconcentrate thallium as much as freshwater fish (Table 5).

Miscellaneous

Early development of sea urchin eggs occurred at concentrations of thallium between 41,000 and 204,000 µg/l (Table 11).

CRITERION FORMULATION

Saltwater Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures. All concentrations herein are expressed in terms of thallium.

Final Fish Acute Value = 3,300 µg/l

Final Invertebrate Acute Value = 37 µg/l

Final Acute Value = 37 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 4,100 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 4,100 µg/l

0.44 x Final Acute Value = 16 µg/l.

No saltwater criterion can be derived for thallium using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

Table 7. Marine fish acute values for thallium

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Sheepshead minnow, Cyprinodon variegatus	S	U	96	20,900	11,426	U.S. EPA, 1978
Tidewater silverside, Menidia beryllina	S	U	96	24,000	13,121	Dawson, et al. 1977

* S = static

** U = unmeasured

Geometric mean of adjusted values = 12,244 ug/l $\frac{12,244}{3.7}$ = 3,300 ug/l

Table 8. Marine invertebrate acute values for thallium (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Mysid shrimp, *Mysidopsis bahia*	S	U	96	2,130	1,804

* S = static

** U = unmeasured

Geometric mean of adjusted values = 1,804 µg/l $\frac{1,804}{49}$ = 37 µg/l

Table 9. Marine plant effects for thallium (Overnell, 1975b)

Organism	Effect	Concentration (ug/l)
Alga, *Dunaliella tertoilecta*	50% inhibition of photosynthesis	4,080
Alga, *Phaeodactylum tricornutum*	50% inhibition of photosynthesis	51,200

Lowest plant value = 4,080 µg/l

Table 10. Marine residues for thallium (Zitko & Carson, 1975)

Organism	Bioconcentration Factor	Time (days)
Soft shell clam, *Mya arenaria*	18	88
Blue mussel, *Mytilus edulis*	12	40

Table 11. Other marine data for thallium (Lallier, 1968)

Organism	Test Duration	Effect	Result (ug/l)
Sea urchin, Paracentrotus lividus		Cessation of early development of fertilized eggs;	
		4 cell stage	204,000
		8-16 cell stage	82,000
		Blastula	41,000

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Mammalian Toxicology and Human Health Effects

EXPOSURE

Ingestion from Water

The major problem in assessing the amount of thallium ingested from water is the inadequate sensitivity of analytical methods for thallium. An almost equally serious problem is the limited amount of information available utilizing even the inadequate methodologies currently available. As a matter of fact, essentially all the information available is to be found in two reports. The first of these is a U.S. EPA study which was conducted in cooperation with the National Heart and Lung Institute and the National Center for Health Statistics. Its main purpose was to delineate the occurrence of inorganics in household tap water and relationships to cardiovascular mortality rates (Greathouse, 1978). The second study was not concerned with average or usual exposures. Rather, it was concerned with worse situations, namely the concentration of thallium in the run-off from slag heaps and holding ponds associated with ore processing and mining operations (U.S. EPA, 1977).

In the first study grab samples of tap water were taken from 3,834 homes. The study began in July 1974 and was completed in December 1975. Multi-elemental analyses were conducted using proton-induced x-ray emission (PIXE). The procedure and its characteristics of precision and sensitivity are described in a separate report (U.S. EPA, 1978). The limit of detectability as applied to water was 0.3 ppb. Samples

of tap water were collected from 3,834 households which were randomly selected from 35 geographic areas by the Bureau of Census to provide a "representative" sample of the U.S. population. Thallium was detectable in only 0.68 percent of the samples. The average thallium concentration, when detectable, was 0.89 ppb. Assuming a water consumption of 2 l/d for the average adult, over 99 percent of adults would consume < 1 µg Tl per day.

So far as worse situations are concerned, the so-called Calspan Report (U.S. EPA, 1978) reviews in great detail the basis for concluding that the leaching of thallium from ore processing operations is the major source of elevated thallium concentrations in water. Thallium is a trace metal associated with copper, gold, zinc and cadmium. Thus, wherever these metals have been mined and processed, an enrichment of the environment with thallium was also suspected to occur. This led to analyses of run-offs from mining and smelting operations involving these other metals. The sensitivity of the analytical methodology for thallium was not as good as for the tap water studies referred to earlier. The overall limit of sensitivity was reported to be 10 ppb, but values down to 3 ppb are reported. It is not clear how this apparent shift in sensitivity came about. Mines and processing operations from Washington and California to New Jersey and Pennsylvania were studied. The highest concentrations reported were 30 ppb in slag run-off near Kellogg, Idaho and 21 ppb in the Colorado River just below the Big Williams River

which drains the Planet Mine, an operation in which copper is extracted from iron ore. It is not at all clear as to how much of the Colorado River thallium came from that particular mine, since this was a generally ore-rich area. The only other source of information as to discharges from Canadian ore operations into streams is Zitko, et al. (1975). He indicates concentrations of 0.7-88 ppb.

Ingestion from Foods

Data concerning the likely intake of thallium from food are about as sparse as from water. So far as thallium in man's usual diet is concerned, only three studies are available. They provide only a limited indication as to what might constitute the total contribution of food to daily intake under normal circumstances. Vegetables (lettuce, red cabbage, green cabbage, leek and endive) averaged 68.2 ppb dry weight (Geilmann, et al. 1960). Assuming 85 percent water content, this would amount to 10 ppb, wet weight. From the same study, bread contained 0.75 ppb, dry weight. The only data concerning thallium in meat report that the concentration in beef rib eye and veal is < 0.5 ppm (Mitteldorf and Landon, 1952). Due to the poor analytical sensitivity, this study is not very helpful. It seems unlikely, however, that meats contribute as much thallium to the total diet as vegetables. This is based on two considerations: 1) vegetarians excrete in their urine four times as much thallium as non-vegetarians (Weinig and Zink, 1967) and 2) the concentration of thallium in human skeletal muscle is only approximately 1 ppb (Weinig and Zink, 1967). This

raises the interesting question as to why vegetables should contain so much more thallium than meat. It is possible that this is related to the relatively high concentration of thallium in fertilizer. Geilmann, et al. (1960) found 37-230 µg Tl/kg in 4 samples of potash fertilizers containing 35-43 percent potassium. Since these studies were conducted on a very limited number of vegetables and fertilizer samples in Germany, it is difficult to estimate just how representative these data are of the situation in the U.S. In any event, if one accepts that most dietary thallium is to be found in vegetables and that 10 ppb is the average fresh weight concentration, an estimate can be made as to the contribution of food to total intake of thallium in man. The average adult consumption of vegetables in the U.S. is estimated at 0.38 kg/d (Toscano, 1975), and the total food consumption is 1.6 kg/d (USDA, 1968). Assuming that the concentration figures cited are correct and that they apply to the average diet of vegetables, the daily intake of thallium from vegetables would be (0.38) (10 µg) or 3.8 µg. As will be shown in the section on Criterion Formulation, this is probably a high estimate. In all probability, the data cited as to concentrations of thallium in a few selected vegetables are really not representative of what is normally eaten in the category of vegetables. Based on the solubility characteristics of thallium, it is also possible that a good deal of thallium is leached out during food preparation.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms.

Since BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States, some have to be estimated. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the 19 major species identified in the survey, the relative consumption of the four major groups can be calculated.

A measured steady-state bioconcentration factor of 34 was obtained for thallium using bluegills (U.S. EPA, 1978) based on whole body, whereas Zitko, et al. 1957 obtained a BCF of 130 in 12 days in Altanic salmon muscle. Zitko and Carson (1975) obtained values of 18 and 12 with the soft shell clam and the blue mussel respectively. The thallium BCF for muscle tissue would probably be similar for saltwater fish and decapods to that for freshwater fish.

Group	Consumption (Percent)	Bioconcentration factor
Freshwater fishes	12	66
Saltwater fishes	61	66
Saltwater molluscs	9	15
Saltwater decapods	18	66

Using the data for consumption and bioconcentration for each of these groups, the weighted average BCF for thallium is 61 in consumed fish and shellfish.

Inhalation

The concentration of thallium in ambient urban air from six major U.S. cities was reported in a U.S. EPA publication by Battelle Columbus Laboratories, in 1971. The concentrations of thallium were given as weighted averages from data from all cities: low, $\leq .02$; high, 0.1 and typical, < 0.04.

The concentration of thallium in fly-ash has been estimated, however, and on this basis the ground level concentration of thallium near a coal-fired plant might be 700 ng/m^3 (Carson

and Smith, 1977). This can hardly be used as a basis for judging usual exposure for the general population. It does suggest a worse case situation however. Assuming inhalation of 20 m^3/d and 35 percent retention of the thallium-bearing aerosol, 700 ng/m^3 would result in the daily absorption of 4.9 ug Tl. The air level in Chadron, Nebraska is stated to be .04-.48 ng/m^3. This may be the more typical level of exposure (Carson and Smith, 1977). Assuming 20 m^3/d inhalation and 35 percent retention, 0.48 ng/m^3 = 3.4 ng Tl/d from air.

Inhalation of thallium in cigarette smoke may, on the other hand, be a very significant source. The urinary excretion of thallium in smokers is about twice that in non-smokers (Weinig and Zink, 1967) and the concentration in cigar stubs was shown to be 57-170 ng/g (Geilmann, et al. 1960), about 20 times the concentration estimated for the diet.

Dermal

The dermal absorption of thallium presumably would normally occur as a result of bathing and from contact with thallium in clothing. It is virtually impossible to estimate the contribution of these potential sources to total intake. Suffice it to say that the concentration of thallium in tap water is less than in body tissues (< 0.3 µg/l vs. ~ 1 µg/kg in tissues). From this it would seem that the net flux of thallium as a result of bathing would, if anything, be outward rather than inward. As to thallium in clothing, there does not appear to be any information.

Exposure to Thallium from Food, Water and Air as a Basis for Estimating Daily Absorption

In summary, this section on various sources of exposure provides only a very broad perspective as to the relative contributions of known environmental media to which the general population is exposed. The most reliable data, fortuitously, concerns thallium in drinking water. It is possible to state with reasonable assurance that > 99 percent of Americans probably absorb < 1 μg Tl per day from this medium. Vegetables may contribute as much as 3.8 μg/day (see Ingestion from Foods) and air is probably an insignificant source, being probably no more than 3.4 ng/day (see Inhalation). If foods other than vegetables are assumed to have a concentration of 1 μg/kg, then their contribution at approximate consumption levels of 1.2 kg (1.6-0.38) would be 1.2 μg/day i.e. (1.2 kg/day) (1 μg/kg Tl in non-vegetable food). Thus, the total daily input based on data reviewed above is $\leq$1 μg (water) + 3.8 μg (vegetables) + .0034 μg (air) + 1.2 μg (non-vegetable food) $\leq$6.0 ug/day. In all of the above, 100 percent absorption is assumed for food and water sources.

PHARMACOKINETICS

Very little is known about the disposition of thallium in man, and most of the limited information concerns cases of clinical poisoning. The reasons for this are twofold. First, thallium has not been thought of as a significant environmental pollutant; therefore, little effort has been made to characterize its metabolism under usual conditions of human exposure. Secondly, the concentration of thallium

in biological media is so low that metabolic studies are extremely difficult to conduct with generally available analytical methods. This latter hindrance applies to man, but not to experimental studies in animals since there exists a very convenient radioisotopic form ^{204}Tl, which has a radiological half-life of approximately 3 years, a readily detectable beta emission and a 70 keV photon owing to K-electron capture.

Since the primary concern of this document is with regard to possible subtle health effects from the low level of thallium to which man is exposed via water, attention will be drawn wherever possible to the distinction between the pharmacokinetics of massive doses and the pharmacokinetics of small doses. Unfortunately, such distinctions can be drawn only from consideration of animal data.

Absorption

The only study of gastrointestinal absorption in man was conducted in a middle-aged woman with terminal osteogenic carcinoma (Barclay, et al. 1953). Following oral administration of a single tracer dose of ^{204}Tl, only approximately 0.5 percent of the dose was excreted in the feces during the succeeding 72 hours, while urinary excretion rose dramatically. This suggests that no bolus of ^{204}Tl passed unabsorbed. Complete absorption of tracer doses of ^{204}Tl administered orally in rats is suggested by the data of Lie, et al. (1960). They found approximately the same fraction of a single tracer dose of ^{204}Tl in various organs at 1, 2 and 7 days regardless of whether the dose was given orally or by any one of four parenteral routes.

There is no information available concerning the deposition and clearance of inhaled thallium aerosols. As with almost all metallic salts, the pattern of deposition of thallium aerosols would depend upon particle size (aerodynamic); and the rate of clearance would depend upon the solubility of the salt. From the report of the Task Group on Lung Dynamics it would be predicted, however, that all salts of thallium (oxide, hydroxide and halide excepted) would be cleared rapidly (days) and that none would be cleared slowly (years) (ICRP, 1966).

The skin as a route of absorption has not received much attention, as is the case with most metallic salts. At one time thallium was applied to the skin as an ointment containing 3-8 percent thallous acetate. Numerous cases of systemic poisoning have been documented to result from this practice (Munch, 1934). This does not mean that skin is a significant portal of entry under usual exposure conditions however. The net movement of thallium across the skin is dependent on the concentration gradient, and the concentration of thallium to which the skin is normally exposed is miniscule in comparison to the concentration under which significant absorption has been demonstrated.

As a summary statement it may be said with reasonable confidence that thallium is completely absorbed from all the usual portals of entry, with the possible exception of the skin.

Distribution

Thallium is widely distributed in the body. It is distributed preferentially to the intracellular space. Based on tracer studies in rats, the apparent volume of distribution has been calculated to be 20 l/kg (Rauws, 1974). This indicates a high degree of concentration in one or more body compartments. To some extent at least, this preferential intracellular distribution is analogous and related to mechanisms which favor the intracellular localization of potassium. Active transport of thallium into erythrocytes, mediated by Na, K-ATPase, has been demonstrated by a number of investigators (Gehring and Hammond, 1964; Cavieres and Elroy, 1974). In spite of the considerable avidity of erythrocytes for thallium, Rauws (1974) estimated that, in rats at least, under steady state conditions 61 percent was distributed to the blood cells as compared to 39 percent in the plasma. Gibson and Becker (1970) similarly reported a cell-plasma ratio of 1.5-2 in rats. The very minor degree of preferential thallium distribution to blood cells is probably due to the very high concentration of potassium in the blood, which competes with thallium for active transport. Factors other than active transport into cells must be operative in the localization of thallium in various organs and systems, since there does exist some organ-specific concentration. Thus, in both conditions of normal thallium exposure and fatal exposure in man, there is a tendency for thallium to concentrate in the kidneys, colon and hair (Weinig and Zink, 1967; Cavanagh, et al. 1974). In other respects the distribution of thallium is not remarkable.

Thallium distributes rather freely from the maternal circulation to the fetus. The fetal-maternal ratios of tracer doses of ^{204}Tl in rats and mice are reported to be, respectively, 0.84 and 0.46 under steady state conditions (Gibson, et al. 1967). These observations were made on gestation days 18 and 19 for mice and rats respectively. It was also found that thallium administered on days 1 and 7 postnatally was distributed in a manner quite like in adult animals. In a later publication these same investigators reported that simultaneous thallium ratios in maternal rat blood plasma and whole fetuses were approximately 15 over a wide range of thallium infusion rates (0.2-6.4 mg/min/kg), indicating that dosage does not seem to alter the kinetics of distribution from mother to fetus (Gibson and Becker, 1970). The high maternal-fetal ratio in this instance is not contradictory to the authors' earlier observation cited above that maternal-fetal ratios in rats and mice are 0.84 and 0.46 respectively since steady state conditions did not prevail in the latter study. Low dietary potassium did not significantly alter maternal-fetal distribution of thallium.

So far as distribution of thallium to the human fetus is concerned, there is essentially no quantitative data. One report indicates that no thallium was found in the 5-month fetus of a woman who died of thallium poisoning. Thallium was demonstrated in various tissues of the mother (Neal, et al. 1935). Absence of detectable thallium in this fetus does not rule out its presence, even at abnormally

high concentrations since the spectrographic method used probably was neither very sensitive nor very precise. It is only possible to surmise that fetal concentrations were lower than maternal concentrations. Richeson (1958) cites one report in which thallium was found in the tissues of a baby whose mother had taken 1.2g thallium at term. The infant died five days after birth.

Excretion

There have been numerous reports of the characteristics of thallium excretion in animals using both tracer doses of ^{204}Tl and rather large (up to 10 mg/kg) carrier doses. By contrast, there are only two studies reported of thallium excretion in man from which may be derived any useful kinetic constants. Worse, each of these two studies involved only a single subject. This serious limitation must be borne in mind in judging the reliability of the safety assessment which ultimately must be made in this document.

The first study traced the fate of an orally-administered tracer dose of ^{204}Tl given to a middle-age woman with osteogenic carcinoma metastatic to the lungs (Barclay, et al. 1953). The dose of thallium given was 0.5 mc, containing 2.3 mg total thallium. In addition, single oral doses of 45 mg non-radioactive thallium sulfate (presumably = 8.7 mg Tl) were also given every 3 days until 225 mg had been administered. Excretion of radioactivity in the urine and feces was determined for the succeeding 5.5 days. It is evident that fecal excretion was inconsequential as compared to urinary excretion (Figure 1). Based on these data, a

first order rate constant of 0.032 day^{-1} was estimated for excretion. The Tl/2 for rate of excretion of the dose would therefore be 21.7d. Based on a rate constant of 0.032 day^{-1}, the amount of thallium remaining in the body at the time of death (24 days after administration of ^{204}Tl) would have been 46.3 percent of the dose from:

$$A = A_o \cdot e^{-kt}$$

where:

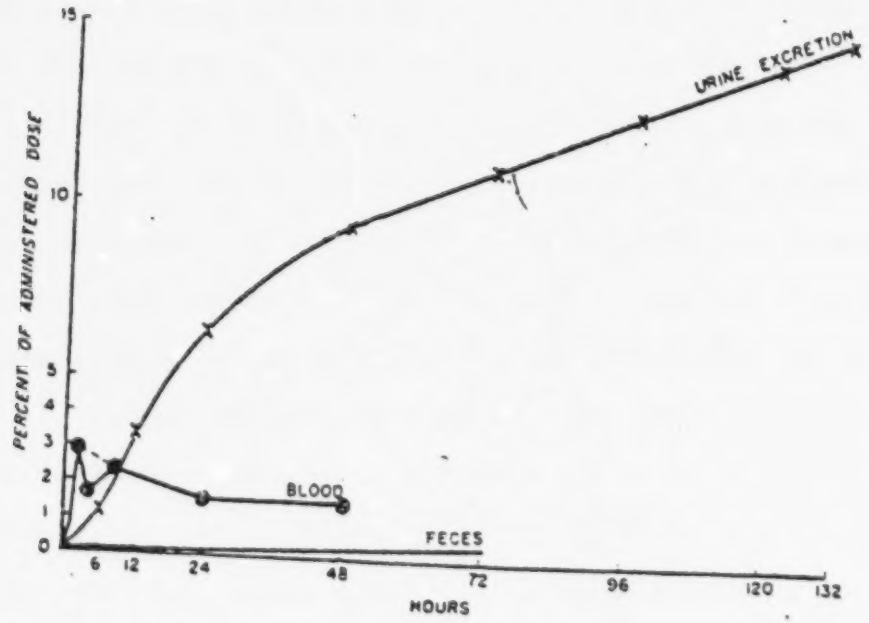

Figure 1. The excretion of ^{204}Tl by a human after oral administration of 500 uc. of activity plus 5-45 mgm. doses of thallous sulfate orally. The level of ^{204}Tl in the blood at 2, 4, 8, 24, and 48 hour intervals after administration of the radioactive isotope is also included (Barclay, et al. 1953).

A = percent dose in body at 24 d

A_o = 100 percent

k = 0.032

t = 24 d

The amount actually recovered in the body at the time of death was stated to be 45 percent. It is not clear how this figure was arrived at. The cumulative urinary excretion of ^{204}Tl, illustrated in Figure 1, has a hyperbolic form during the first 48 hours, consistent with a first order rate process. Subsequently, the cumulative urinary excretion is linear with time. This is inconsistent with animal studies and with the only other human study discussed below, wherein a first order rate process prevails, even months following dosing. The small supplementary doses of thallium sulfate given subsequent to the single dose of ^{204}Tl would not likely have altered the form of the excretion curve. These supplementary doses no doubt increased total thallium excretion, but this would not affect the rate of ^{204}Tl excretion since dilution of the ^{204}Tl pool with "cold" thallium would precisely cancel any enhancement of ^{204}Tl excretion resulting from the increased total thallium concentration presented to the kidney.

The only other paper which sheds light on the kinetics of thallium excretion in man was a report of a single case of poisoning (Innis and Moses, 1978). Approximately four weeks following the likely time of intoxication a series of urine analyses for thallium were performed. These data are presented in graphic form (Figure 2). The estimated Tl/2 for urinary

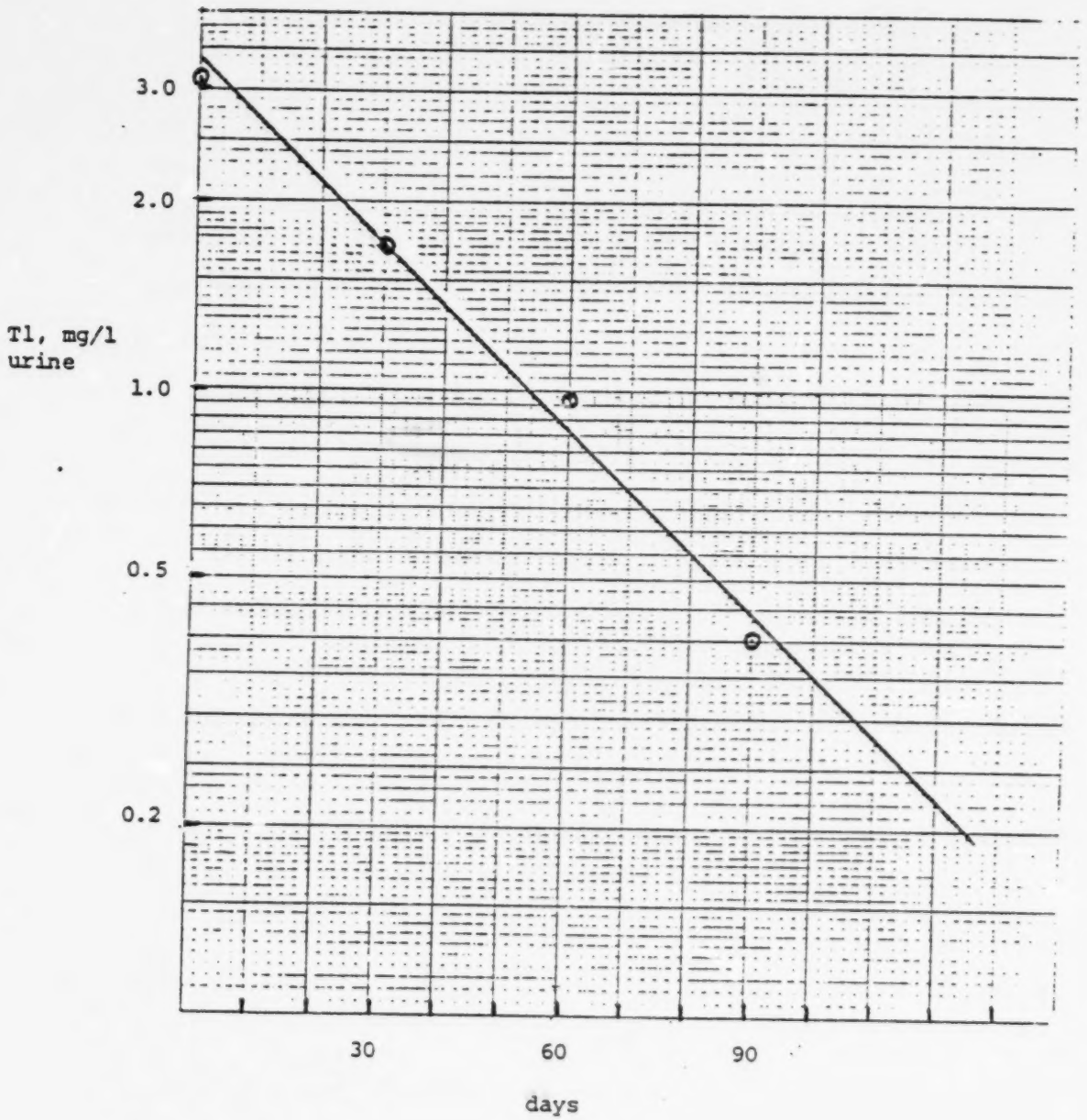

Figure 2. The excretion of thallium in the urine of a patient, beginning approximately four weeks after thallium intoxication (Calculated from Innis and Moses, 1978).

excretion was 30 days ($k = .023\ day^{-1}$).

The discrepancy in rate of urinary loss of the body burden in the two above-described cases ($k = .032$ vs. $k = .023$) is not remarkable. The rate constant calculated for the first subject was based on excretion data which behaved in a kinetically anomalous fashion. On the other hand, the rate constant calculated for the second subject may have been influenced by the fact that she was experiencing clinical manifestations of thallium poisoning. It is known from experimental studies in rats that the rate of body clearance of thallium is considerably slower following a toxic dose than following a tracer dose. Thus, Gehring and Hammond (1967) reported a rate constant for total thallium excretion of $0.0353\ day^{-1}$ in rats receiving a single iv injection of 10 mg Tl/kg as compared a rate constant of $0.0790\ day^{-1}$ rats receiving a tracer dose ($<$ 0.1 mg Tl/kg). These constants were for animals on low dietary potassium. When dietary potassium was high, tracer doses were more rapidly excreted ($k = 0.146\ day^{-1}$). In summary, for people not experiencing overt signs of thallium poisoning, it seems that the appropriate rate constant lies between 0.032 and $0.023\ day^{-1}$. The slower rate constant (0.023) will be assumed in the criteria formulation for purposes of calculating the accumulation of thallium in man since this represents the more conservative approach.

It should be noted in passing that the excretion of thallium in animals differs from the excretion in man in two respects. To begin with, the rate of excretion is much

more rapid in animals. The example cited above wherein the rate constant for total excretion in rats on a high potassium diet was 0.146 day^{-1} has been confirmed by others. Lie, et al. (1960) calculated a rate constant of 0.210 day^{-1} for rats receiving single tracer doses and Rauws (1974) calculated a rate constant of 0.173 day^{-1} in rats receiving single doses of 10 mg/kg. Thus, the average from these three studies was 0.18 day^{-1}. The other major difference between man and animals is as to the relative contribution of fecal and urinary excretion. Whereas the gastrointestinal tract seems to be a very minor excretory pathway in man, the rate of fecal excretion is about 3-4 x the rate of urinary excretion in the rat (Gehring and Hammond, 1967; Lie, et al. 1960). In the rabbit the contribution of the two routes of excretion is about equal (Truhaut, 1952).

The rate of urinary excretion under steady state conditions of intake should reflect fairly accurately the rate of total thallium absorption. This proves to be an extremely important consideration in light of the fact that reliable estimates of intake based on known concentrations in food, air and water are virtually non-existent. The only published estimate of total dietary intake is < 2 µg/d (Hamilton and Minski, 1972-1973).

Four groups of investigators have reported reasonably useful data regarding the concentration of thallium in the urine of persons with no known unusual exposure. Williams and Riegert (1971) reported urinary thallium in a group of workmen suspected of having thallium poisoning. Their analytical method was not described and probably was not

very sensitive. The range of urinary thallium was 3-15 µg/l, but half of the samples were registered as negative (presumably < 3 µg/l). Unaffected workers had similar levels. This study is of very limited use because of uncertainties regarding the reliability of the analytical method and because it is not at all certain that the unaffected workers had essentially normal thallium exposure. The second study was performed using an organic solvent extraction procedure and atomic absorption spectrometry (Kubasik and Volosin, 1973). The limit of detection was 1.5 µg Tl/l of urine. Twenty samples of urine from normal subjects were all negative for thallium. It would seem from these results that the "usual" value for thallium in the urine of normal people is < 1.5 µg/l.

The last two papers in this series are the most significant in that methodologic sensitivity was sufficiently good to yield finite numbers for the concentration of thallium in urine. In the first of these two investigations (Weinig and Zink, 1967), the subjects were categorized according to dietary and smoking habits. It appeared that both smoking and vegetarian dietary habits tended to increase thallium excretion and perhaps dietary intake (Table 1). In the second study (Goenechea and Sellier, 1967) no such distinction is made and the average urinary concentration of thallium is somewhat lower though similar (Table 2). From the data in the last three papers it seems safe to assume that the concentration of thallium in urine seldom exceeds 1.5 µg/l. The discrepancy between the data in the last two studies, 0.81 vs. 0.23 µg/l, cannot be explained. Even if one assumes

TABLE 1*

Thallium Concentration in the Morning Urine of Vegetarians, Smokers and Non-smokers with Normal Diets

Subject	Sex	Age, y.	Urine sp. g.	Tl, ng/g	Ave. Tl, µg/l for group[b]
Vegetarian	F	40	1.024	1.34	
" "	M	43	1.034	1.69	1.28
" "	M	12	1.032	0.92	
Smoker	M	28	1.019	1.42	
"	M	25	1.023	0.40	0.82
"	M	24	1.018	0.69	
Non-smoker	M	26	1.008	0.13	
"	F	60	1.025	0.39	0.34
"	F	48	1.030	0.53	
				overall average	0.81

[a]urine specific gravity

[b]calculated from the authors' data in the table

*Weinig and Zink, 1967

TABLE 2*

Naturally-Occurring Thallium Concentration in the Urine and Feces of Humans Under Physiological Conditions

Case	Urine, µg/kg	Feces, µg/kg
1	0.1 0.4	0.6 3.0
2	0.1	b
3	0.2	b
4	0.1	b
5	0.1	b
6	0.3	0.1
7	1.0	b
8	0.2	b
9	a	a
10	a	0.1
average[c]	0.23	

[a]below detectable limit, which is 0.02

[b]not determined

[c]assumes urine samples below detectable limit = 0.02 µg/kg

*Goenechea and Sellier, 1967

that the higher of the two figures is correct and that average daily urinary excretion is 1.5 l, average daily thallium excretion in the urine would be 1.2 μg (0.81 μg/l x 1.5 l).

Total Daily Excretion of Thallium as a Basis for Estimating Daily Absorption

Is is useful to estimate total daily excretion of thallium since this can reasonably be assumed to be the same as total daily absorption, at least under steady state conditions. To the daily excretion via the urine must be added the following miscellaneous routes:

1) gastrointestinal excretion (including cell exfoliation)
2) hair
3) exfoliating epithelium of the skin
4) sweat

The contribution of gastrointestinal excretion is probably very minor in man, at least based on the data of Barclay, et al. (1953). From Figure 1 it can be estimated that cumulative fecal excretion was 0.5 percent of the dose of ^{204}Tl at 72 hours whereas cumulative urinary excretion at the same time was approximately 11 percent of the dose. On this basis, one might add to the average urinary excretion an additional increment of 1.2 x 0.5/11 = 0.06 μg/d.

So far as excretion via hair is concerned, it was reported by Barclay, et al. (1953) that at autopsy 7 percent of the original dose of ^{204}Tl was localized in scalp hair. During this same period 55 percent of the original dose had been lost by other excretory routes. Minor loss of ^{204}Tl via hair was also reported in rats (Lie, et al. 1960). Seven

days following a pulse dose of ^{204}Tl, approximately 75 percent of the radioactivity had been excreted in the urine and feces. Only 1.56 percent of the residual amount was localized in hair. Assuming that total excretion via hair = 2X scalp hair excretion, 14 percent could conceivably have been removed from the body in this manner. An additional increment of 1.26 μg x 14/55 or 0.32 μg results.

Exfoliation of skin and sweat probably do not contribute significantly to total thallium excretion, at least probably not more so than the gastrointestinal tract which has a larger surface area than the skin, a very rapid turnover rate of epithelium and a high rate of secretory activity. It would seem conservative to assign to the skin an excretory role similar to the role of the gastrointestinal tract. In summary, total excretion of thallium per day is probably as follows in adults not exposed to unusual sources of thallium:

Excretory route	μg Tl/d
urine	1.20
feces	0.06
hair	0.32
skin and sweat	0.06
total	1.64

Body Burden of Thallium as a Basis for Estimating Daily Absorption

There is an alternate basis for estimating daily absorption of thallium. It begins with certain assumptions which seem correct. First, it is assumed that the excretory process is essentially first-order, wherein the rate of excretion

is proportional to the amount in the body at that time. Second, it assumes that input is fairly constant - essentially zero order. For the steady state condition, the following relationship exists:

$A_B = \frac{A_d}{k}$ where:

A_B = amount in the body

A_d = amount absorbed per day

k = elimination constant (day^{-1})

The amount of thallium in the body (A_B) of persons not unduly exposed has been estimated to be 100 µg per 75 kg (Weinig and Zink, 1967). Using the elimination constant of Innis and Moses (1978), k = 0.023, the daily absorption of thallium to attain a steady state body burden of 100 µg would be:

$100\ \mu g = \frac{x}{.023}$ or $x = 2.3\ \mu g$.

That is approximately 1.4X the value obtained using the estimated sum of excretion by all pathways, and approximately 0.4 times the intake value derived from estimates of input from food, water, and air. Since the estimated body burden is based on data from only two cadavers, the small difference in estimated daily absorption is not surprising. Order-of-magnitude agreements using two different approaches to the problem of intake are about all one can expect given the small amount of hard data available.

EFFECTS

Acute, Sub-acute and Chronic Toxicity

The vast majority of the cases of adult human poisoning have been acute, usually involving single doses, taken by reason of homicidal or suicidal intent. Poisoning in children

also is acute, resulting from ingestion of thallium-containing rat and ant bait or from its therapeutic use as a depilatory agent. It is possible to estimate at least roughly the minimum lethal dose. As for the minimally toxic dose, the former practice of using thallium as a depilatory agent makes it possible to make an estimate, at least for children.

Cavanagh, et al. (1974) investigated a homicidal attempt on three men, two of whom died after being given 930 mg thallous acetate (721 mg Tl). The third man survived a dose of 310 mg (240 mg Tl). In another series of seven cases of suicidal attempts, four survived the consumption of one tube of Zelio Paste, 263 mg Tl, with signs of poisoning, two survived after eating two tubes of Zelio Paste or 526 mg Tl, and one died after eating five tubes of Zelio Paste (Grunfeld and Hinostroza, 1964). Assuming an average weight of 70 kg, the average toxic, non-fatal dose for adults is about 4-8 mg/kg and the minimal fatal dose is probably somewhat less than 10 mg/kg. The minimal acute lethal dose is quite similar for a variety of animal species and the range from the highest non-lethal dose to the lowest lethal dose also is quite narrow (Table 3) (Downs, et al. 1960).

Based on the limited data available, children seem to be no more sensitive to the acute toxic or lethal effects of thallium than adults. In a series of 8,006 children estimated to have been given single oral doses of 3.1-7.8 mg Tl as thallous acetate as a depilatory, 447 (6 percent) became ill and eight (0.1 percent) died (Munch, 1934). Given the imprecise nature of reports as to incidence of toxic

TABLE 3

Acute Toxicity of Thallium Compounds*

Route	Species	Thallous Acetate #	& Sex	lethal range** mg Tl/kg	Thallic Oxide #	& Sex	lethal range** mg Tl/kg
iv	rabbit	7	F	12-20	3	F	24-39
ip	rabbit	9	F	8-13	3	M	30-60
	guinea pig	25	M,F	4-7	3	F	10-30
	rat	41	F	13-20	41	F	62-92
po	rabbit	4	F	12-19	3	M	10-30
	guinea pig	4	M	8-12	10	M,F	3-5
	rat	37	F	18-29	42	F	9-20
	dog	3	M,F	10-20	3	M	20-30

*Downs, et al. 1960.

**lethal range = highest non-lethal dose - lowest dose showing any lethality during 14-day period.

effects, it is of course quite possible that substantially more than 6 percent of the children in this series experienced signs or symptoms of poisoning. It is not even known how consistently the therapeutic objective of alopecia was attained in this series of cases.

Acute thallium poisoning is a disease entity which has been widely described. The initial signs and symptoms involve primarily the gastrointestinal tract and peripheral nervous system. Alopecia does not generally occur until several weeks following intoxication. Indeed, in fatal cases death may supervene before alopecia occurs. The detailed description of three cases of acute poisoning by Cavanagh, et al. (1974) is rather typical of what has been described by many other investigators (see, for example, Paulson, et al. 1972; Papp, et al. 1969). Initially, the subject experiences gastrointestinal pains, diarrhea, and vomiting. This is followed by paresthesia of the upper and lower limbs, dizziness, and facial weakness. These signs first appear in 2-5 days. A frequent complaint is pain and tenderness of the lower limbs, particularly of the knees. Dysphagia and dyspnea also are commonly reported. Sensory impairment occurs frequently. The cranial nerves as well as the spinal nerves are affected. The central nervous system also is affected to varying degrees. Attention span is reduced; somnolence and delerium or coma may occur. Various abnormalities of cardiac function have been reported, including sinus tachycardia and flattening or inversion of the T-wave. These and other cardiac effects have been variously attributed

to vagus involvement and to myocardial damage. The electroencephalogram is frequently abnormal (Cavanagh, et al. 1974). These effects and others occur in various combinations. Chamberlain, et al. (1958) summarized the incidence of effects in their series of 14 cases in children (Figure 3), as did Grunfeld and Hinostroza (1964) in a series of adult cases (Figure 4).

Although acute poisoning is a somewhat protracted disease, with effects lingering for several months, the prognosis for full recovery in adults seems to be good. Such does not appear to be the case in children. In a follow-up study of 72 cases, Reed, et al. (1963) found that 26 of 48 had neurologic abnormalities when they were followed up for an average of 4 years. The neurologic abnormalities found at follow-up usually represented persistence of signs found during the initial stages of the disease (Table 4). It should be noted that mental abnormalities and muscle weakness or paralysis actually increased in incidence during the follow-up period.

It is not surprising that acute thallium poisoning should lead to irreversible damage or at least to only slowly-reversible damage to the central and peripheral nervous system. Degeneration of peripheral nerve fibers and chromatolysis of motor nerve cells were frequently reported in man (Munch, et al. 1933; Gettler and Weiss, 1943) and in animals (Zook and Gilmore, 1967; Zook, et al. 1968).

So far as subacute and chronic thallium poisoning in man are concerned, there are very few reports of any kind and those which are available provide little information

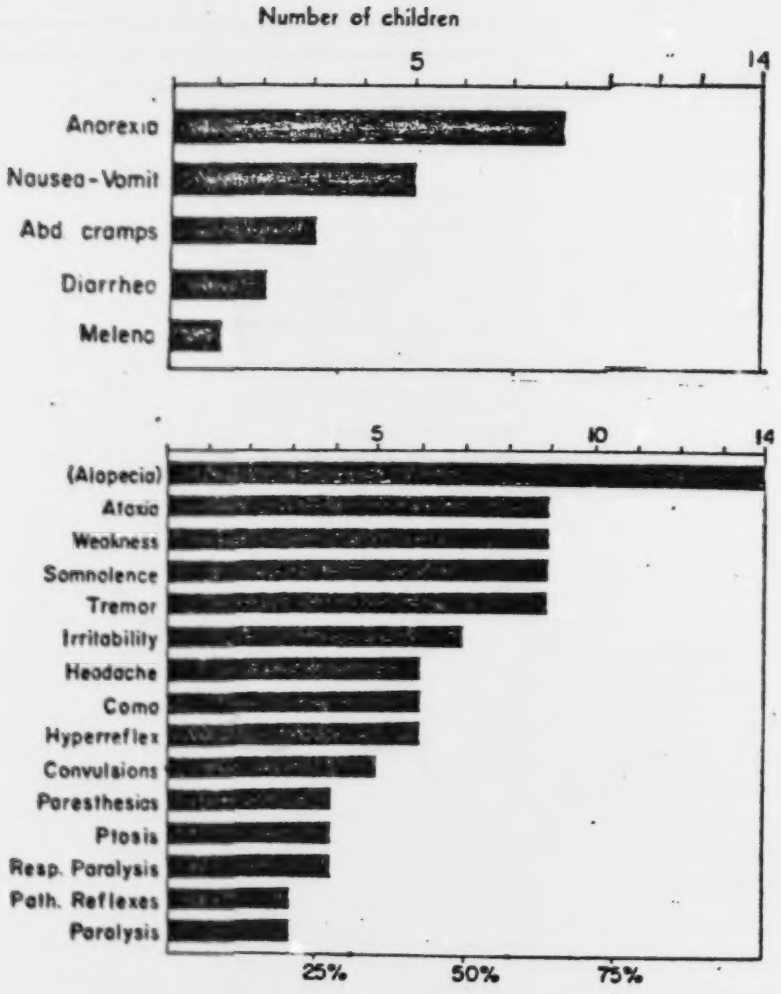

Figure 3. Incidence of gastrointestinal (top) and neurologic signs and symptoms of thallo-toxicosis in children (Chamberlain, et al. 1958).

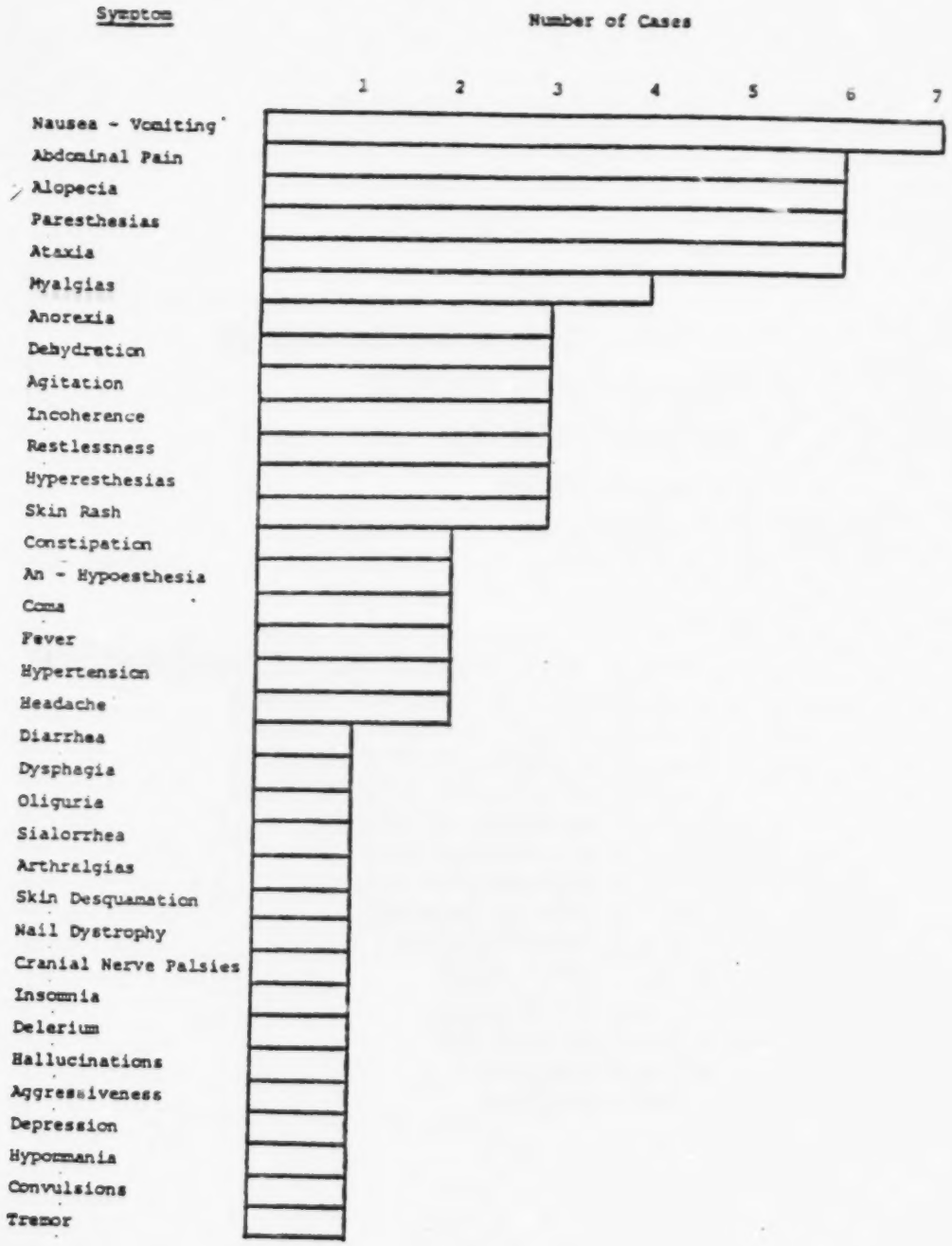

Figure 4. Signs and symptoms in seven cases of thallotoxicosis (Grunfeld and Hinostroza, 1964).

TABLE 4

Percent of 26 Patients with Abnormalities at Follow-up Stage (Southern Texas Thallotoxicosis Study, 1954-1959)*

Symptoms	Acute Stage of Illness, %	Follow-up Stage, %
ataxia	81	23
tremor	57	19
abnormal reflexes	62	38
convulsions	27	15
abnormal vision	15	4
mental abnormalities	15	58
abnormal movements	15	8
muscle weakness or paralysis	4	15

*Reed, et al. 1963.

as to duration of exposure, level of exposure as reflected in thallium concentrations, or doses in either the external environment or in the affected subjects. In one brief report concerning 13 men exposed 3-4 months, the signs and symptoms were pains in the legs, weariness, loss of hair, disturbance of sensation, psychic trouble, albuminuria and nephritis (Meyer, 1928). Generally speaking, these findings correspond to the usual description of acute poisoning. The author also reports that lymphocytosis was a constant finding. Gettler and Weiss (1943) reported that in two cases of chronic poisoning the only symptoms observed were pain in the legs, mild symptoms resembling those of encephalitis, alopecia and oliguria. The suggestion that renal damage is a feature of chronic poisoning is not surprising. In the description of acute cases of poisoning, frequent reference is made to manifestations of renal damage (Fischl, 1966). Postmortem evidence of renal damage, at least in acute poisoning, also has been reported (Gettler and Weiss, 1943). Finally, there also is one report of a case of chronic intoxication in a man exposed 24 years. The main effects were loss of hair, ascending polyneuritis and disturbances of speech and vision (Egen, 1955).

Rats fed thallous acetate in their diet for 105 days experienced no reduction in weight gains at concentrations of 5 and 15 ppm; 30 ppm, however, proved fatal to approximately half of the animals. The only toxic effect noted at 15 ppm was loss of hair (Downs, et al. 1960). It was first noted at two weeks. It must be recognized, however, that

there has been very little effort to search for more subtle effects at exposure levels below those causing alopecia. The only study of the toxic effects of truly chronic administration of thallium in animals ($>$ 90 days) was reported by Tikhonova (1967). In this instance, thallium administration in rabbits resulted in paralysis and pathological changes in the liver, kidneys and stomach mucosa.

In summary, it seems from the limited number of reports that regardless of whether thallium intake occurs in one dose or over several months, the effects are qualitatively very similar, if not identical. It is not possible to state with any degree of certainty which of the many effects reported is the one to which man is most sensitive. It would seem, however, that in cases of acute poisoning in man alopecia is the most consistent effect among those surviving more than two weeks. Thus in the series of children studied by Chamberlain, et al. (1958), this was clearly the case. In the series of adult cases reviewed by Grunfeld and Hinostroza (1964), (see Figure 4), nausea and vomiting occurred in one case where alopecia did not occur, but that subject survived only 5 days after ingesting thallium. Among documented cases of chronic poisoning no specification as to the frequency of various signs and symptoms has been recorded. In summary, the most consisently reported effect is alopecia. Unfortunately, consistency cannot be equated a priori with sensitivity.

Synergism and/or Antagonism

Potassium has long been known to exhibit significant interactions with thallium, both in the pharmacokinetic sense and as to toxic interactions. Lund (1956) first demon-

strated that potassium increases the renal clearance of thallium. Mullins and Moore (1960) demonstrated that the influx and efflux patterns of thallium in frog muscle were quite similar to the fluxes of potassium. Gehring and Hammond (1967) extended these earlier observations to show that potassium markedly enhanced the rate of thallium excretion in both rats and dogs, mainly in the urine. Salivary secretion of potassium, when stimulated with deoxycorticosterone, was accompanied by a corresponding increase in thallium excretion. Potassium also increased somewhat the acute LD50 of thallium, suggesting mobilization from the receptor sites responsible for the toxic effects.

As a result of these studies in animals, the use of potassium was instituted in the management of thallotoxicosis in man. Results have been somewhat equivocal. The use of potassium in the management of thallotoxicosis does result in some increase in the urinary excretion of thallium, but this mobilization is accompanied by a temporary accentuation of the neurological signs and symptoms (Innis and Moses, 1978; Papp, et al. 1969).

Several other interactions have been reported, but their significance is difficult to evaluate. Levkovitch (1938) reported that ambient temperature has an effect on thallium toxicity (sheep and rabbits), and that confinement and dietary restriction enhanced toxicity. Levander and Argrett (1969) observed that thallium reduced the exhalation of volatile selenium metabolites, an action shared with mercury and arsenic. Unlike arsenic, however, neither thal-

lium nor mercury increased biliary excretion concomitantly.

Teratogenicity

There are two reports in the literature which suggest a teratologic effect of thallium. The first of these was a study of the effect on chick embryos (Karnofsky, et al. 1950). Tl_2SO_4 (0.4 - 0.7 mg/egg) was administered during incubation. The primary defect produced was achondroplasia. Thallium also produced early embryonic death and reduced embryonic size. Thus, the study did not fulfill the usual criteria for teratogenesis wherein the effect must be demonstrable at doses not otherwise grossly toxic.

Only one study of thallium teratogenesis in mammalian species has been reported. Gibson and Becker (1970) studied the teratogenic effects of thallium in rats under conditions of both low and normal dietary potassium. Thallium administered intraperitoneally to the mothers early (d. 8,9,10) at 2.5 mg/kg/dose or late (d. 12,13,14) at 2.5 and 10 mg/kg resulted in reduced fetal weight and in increased incidence of teratologic effects (hydronephrosis and missing or non-ossification of vertebrae). It was observed that at both dosage levels thallium caused maternal toxicity as manifested by diarrhea, lethargy, irritability, poor hair luster and body hair loss. One interesting aspect of this study was in regard to the effects of dietary potassium deficiency. A low-potassium diet materially increased the toxicity of thallium to the dams and was of itself teratogenic, but it did not potentiate the teratogenic effect of thallium. Given the types of malformation reported, the evidence of

maternal toxicity and the reduced fetal weights, it is quite likely that these effects were due to delayed fetal maturation (see, for example, Kimmel and Wilson, 1973). Thus, neither of the studies reporting teratogenic effects is credible. In both cases thallium was administered by a parenteral route and in both cases general fetotoxic effects were apparent. Thus, it is impossible to distinguish teratogenicity from a more general toxic effect.

Mutagenicity

No information could be found concerning the mutagenicity of thallium.

Carcinogenicity

There are no published reports on the carcinogenicity of thallium; however, there are two carcinogenicity studies on-going at the time of this document's preparation. Carcinogenicity/mutagenicity/teratogenicity evaluations of thallium sulfate are being conducted by Litton Bionetics under EPA contract; Sprague-Dawley rats are being fed thallium sulfate in the diet at three dose levels. The National Institute for Occupational Safety and Health in Cincinnati, Ohio is investigating the carcinogenicity of thallic oxide by inhalation in rodents.

Without any implications as to non-carcinogenicity, it is of interest to note that thallium has mild anti-carcinogenic effects, along with other metals of Group IIIa (Adamson, et al. 1975).

CRITERION FORMULATION

Existing Guidelines and Standards

There is a threshold limit value of 0.1 mg/m^3 for thallium in workplace air (ACGIH, 1971). This value is based on analogy to other highly toxic metals. This standard which has been adopted by the Occupational Safety and Health Administration (OSHA), is the same as for East Germany and West Germany (Winell, 1975). The U.S.S.R. standard is 0.01 mg/m^3. No criteria have been developed for irrigation water, drinking water, fresh water or other media.

Current Levels of Exposure

It is extremely difficult to specify current levels of exposure for either man or animals because of the scarcity of good data. This is due to the fact that analytical methods which have been applied to the problem have generally not been sufficiently sensitive for determination of thallium in major media (air, food, water) or in normal man. This is not to say that adequate methods do not exist. For example, the mass spectroscopic-isotope dilution procedure used by Weinig and Zink (1967) could detect thallium in urine in the range of .01-0.1 ng/g. There probably has not been sufficient motivation to develop alternate adequately sensitive methodology to define human exposure adequately in the normal range.

Certain approximations as to usual human exposure are possible. Thus, based on one extensive study it seems that tap water seldom exceeds 0.3 µg Tl/l (Greathouse, 1978). Assuming that the average adult consumes 2 liters of water per day, total input would be somewhat less than 1 µg/d.

Even in the worst conditions of water pollution, the concentration of thallium probably seldom exceeds 30 µg/l (U.S. EPA, 1977). These conditions occur in the immediate vicinity of ore processing operations and possibly in streams draining ore-rich soils, e.g. the Colorado River as it courses through western Arizona.

Limited data on thallium in vegetables suggest that these, as a class of food, may have considerably higher concentrations of thallium, perhaps 10 µg/kg wet weight, than other classes of foods (Geilmann, et al. 1960). Bread and muscle, for example, contain 1 µg/kg or less. This may explain the observation that vegetarians excrete considerably more thallium in the urine than non-vegetarians. Assuming that total food consumption is 1.6 kg/d, (USDA, 1968), that 0.38 kg is in the form of vegetables, and that the remainder has a concentration of only 1 µg/kg, total thallium intake would be (0.38) (10) + (1.2) (1) = 5 µg. This estimate probably is on the high side since prepared vegetables would likely have less thallium than raw vegetables due to leaching of thallium into water during cooking.

So far as ambient air as a source is concerned, the single largest anthropogenic source of thallium is considered to be stack emissions from coal-fired plants. It has been estimated that flue gas would contain about 0.7 mg/m^3, with a likely ground level concentration of 0.7 $\mu g/m^3$. Given that a large factor of dilution would result by dispersion from the base of a stack, it seems unlikely that

the contribution of coal combustion to thallium in ambient air would be significant. The highest measurement of thallium reported in ambient air indicated a range of 0.04-0.48 ng/m^3 (Carson and Smith, 1977).

Inhalation of thallium in cigarette smoke may, on the other hand, be a very significant source. The urinary excretion of thallium in smokers is about twice that in non-smokers (Weinig and Zink, 1967) and the concentration in cigar stubs was shown to be 57-170 ng/g (Geilmann, et al. 1960), about 20 times the concentration estimated for the diet.

Total intake in the general non-smoking adult population calculated on the basis of exposure data thus would consist of no more than 1.0 µg/d from water and no more than 5 µg/d from food, even assuming that virtually all ingested thallium likely is absorbed.

The total daily assimilation of thallium by adults in the general population has been also arrived at by consideration of excretion data and estimated body burden. The estimated daily intake arrived at by consideration of food and water exposure and by these other two methods is as follows:

Basis	Estimated Daily Adult Intake
Food, air and water exposure	$\leq$6 µg/d
Excretion data	1.64 µg/d
Body burden data	2.3 µg/d

Special Groups at Risk

From the standpoint of age, there is no basis for believing that children are more susceptible to thallium intoxication than adults. Children, however, experience neurological sequelae, while adults do not. There is no reason for suspecting either that the fetus is unusually sensitive. Essentially nothing is known regarding sex differences in susceptibility. One study in rats indicated that females are more resistant to sub-chronic toxicity than males. From the standpoint of exposure hazard, it would seem that smokers may have twice as great a level of thallium intake as non-smokers. This suggestion is based solely on data concerning urinary thallium excretion in six people and on very limited information concerning thallium in cigars. Obviously, people occupationally exposed to thallium may constitute a special risk category, but this matter has received little attention, largely because total annual industrial production of thallium is so small, probably about 0.5 tons. In the U.S., the main source of poisoning, thallium-containing rodenticides and insecticides, has been terminated. The manufacture and distribution of these products is no longer permitted.

Basis and Development of Criterion

The proposed criterion for thallium in water is derived from 1) estimated least toxic level on chronic intake in man, 2) introduction of a margin of safety and 3) relative contribution of water and other media to total daily intake in the general population.

In estimating the least toxic level of intake, the effect to which man is most sensitive probably is alopecia.

Loss of scalp hair in man and of body fur in animals seems to occur at somewhat lower levels of intake than any other known effects. This is not so clearly the case in adults as in children and animals. There is, however, no great difference between the acute or chronic dose causing alopecia and the dose causing neurologic effects. The least daily amount of thallium which, when taken for a lifetime, will cause alopecia can only be estimated on the basis of sub-chronic animal exposure data combined with some kinetic considerations. From Downs, et al. (1960) it is estimated that the least toxic sub-chronic level of intake in rats was 1.6 mg Tl/kg/d. Alopecia occurred in 2 weeks as a result of the administration of thallium at 12 ppm in the diet. In the following the average weight of rats is derived from inspection of Figure 1 (male rats) in the authors' report; the average food was assumed to be 10 g at that weight:

1) least toxic dietary level = 15 ppm thallous acetate
   = 12 ppm thallium (12 µg/g)

2) average weight of rats = .075 kg

3) average diet consumption = 10 g/d

   (12 ug/g) (10g) = 240 µg Tl/d/.075 kg

   = 1.6 mg/kg/d

In spite of continuous intake for 105 days, animals receiving a modestly lower level (one-third) showed no alopecia or other effects. At the least toxic dose level, effects occurred within two weeks or they did not occur with continued intake. This is consistent with the rapid turnover of thallium in rats and the consequently rapid attainment of a steady state level of thallium in the body. Within two weeks,

a steady state is virtually achieved since 14 days represents more than three half-lives for thallium clearance from the body. Thus, steady state for input vs output:

$$A = \frac{1.6 \text{ mg/kg/d}}{.18 \text{ day}^{-1}} \quad ; \; A = 8.9 \text{ mg/kg}$$

where:

A = amount in 1 kg body weight

k = constant for rate of excretion

At 14 days

$$A = \frac{1.6 \text{ mg/kg/d}}{0.18 \text{ d}^{-1}} \cdot (1-e^{-0.17 \cdot 14})$$

$$A = \frac{1.6}{.18} \cdot (1-.09)$$

A = 8.1 mg/kg (compared to 8.9 above)

Extrapolation of this minimal toxic level of 1.6 mg/kg/d to man requires one assumption, that man and rat are about equally sensitive to the toxic effects of thallium. This seems reasonable. A comparison of minimal acute lethal doses is possible; 13-20 mg/kg in rats (Table 3) and 8-10 mg/kg in man. However, in order for man to attain the same toxic level in the body as the rat, the required intake is much smaller because the turnover of thallium in the body is much slower (k = 0.18 in the rat vs k = 0.023 in man). Thus, in man, the dose required to attain a minimally toxic steady state whole body concentration of thallium would be only 0.20 mg/kg/d from:

$$\frac{k \text{ (man)}}{k \text{ (rat)}} = \frac{A_D \text{ (man)}}{A_D \text{ (rat)}}$$

where: A_D = mg Tl/kg/d

= 1.6 mg/kg (rat)

Because of the tenuous nature of the data on which these calculations are based, it must be accepted that the

minimal toxic level of chronic exposure may be lower than estimated here. Even assuming that the minimal toxic dose is actually lower than estimated, the spread between toxic intake and man's current level of intake is considerable. It is estimated that the usual input from drinking water, food and air is no more than 6 μg/d for an adult weighing 70 kg. This is in contrast to a minimal toxic level of 15.4 mg/day for a person weighing 70 kg. The safety factor is thus approximately 2500 ($\frac{15,400\ \mu g/d}{6.0\ \mu g/d}$).

So far as a safe level of thallium in drinking water is concerned, there does not seem to be any reasonable possibility that even the most thallium-polluted waters would have a toxic effect. In the worst case identified by Zitko, et al. (1975), the concentration of thallium was 88 μg/l. Assuming that this were a human water supply, the daily input at 2 l. per day would be only 176 μg Tl, 0.011 times the minimally toxic input calculated in this document.

The great difference between estimated minimally toxic exposures and current total exposure in the general population is reassuring. One cannot be totally sanguine, however, since there is a paucity of chronic data, including mutagenicity, teratogenicity and carcinogenicity. For that reason it seems prudent to keep levels of exposure at or below their present levels. From the data available, it would seem that few if any public water supplies would ever contain more than 4 μg/l. This seems like a reasonable standard which would protect against gross excursions beyond the usual range of thallium in water, which appears to be of the order 0.1-1 μg/l. This level also provides a safety factor

of three orders of magnitude - 10^3. This is in agreement with well-accepted guidelines of the NAS (1977) for calculating a safety factor which is used in the case of compounds where there are: "No long-term or acute human data. Scanty results on experimental animals. No indication of carcinogenicity." (NAS, 1977). Consumption of 2 liters of water per day and 18.7 grams of fish and shellfish products/day with an average bioconcentration factor of 61 from ambient waters containing 4 µg/l of thallium results in an intake of 12.56 µg Tl/d, compared to the estimated minimal toxic dose of 15,400 µg/d.

In summary form, the dose-response scale for man is estimated to be as follows:

Dose	
8-10 mg/kg	minimally lethal single dose
220 µg/kg/d	minimally toxic dose over a lifetime
1000 µg/kg/d	category 3 safety factor recommended by NAS according to available data
4 µg/l. H_2O	recommended standard
20 µg/l 70kg/d	thallium consumption @ 10 µg/l
1 µg/l	probable limit for > 99 percent of U.S. tap waters
$\leq$+1 µg/d	probable current level of daily adult thallium consumption from drinking water
15.4 mg/d	acceptable total daily intake of thallium from air, water, and food

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